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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,875	03/22/2002	Midori Shima	2462-132US	8702

7590 05/18/2005

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,875	SHIMA ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-18 and 20* is/are rejected.

7)☒ Claim(s) *17,18 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of April 18, 2005 is acknowledged. It is acknowledged that no claims have been deleted, amended, or added. Claims 14-18 and 20 are pending and are hereby reconsidered.

Specification-Objections

All objections to the specification are maintained, as no amendments have been made. Applicant's state that "The objections to the specification... will be addressed upon acknowledgment that the claims are otherwise directed to allowable subject matter.

Claims-Objections

Objections to the claim set and Claims 17, 18, and 20 are maintained, as no amendments have been made. Applicant's state that "The objections to the... claims will be addressed upon acknowledgment that the claims are otherwise directed to allowable subject matter.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejection of Claim 20 under 35 U.S.C. 112, second paragraph, for the reasons stated in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

> "Pepsin, trypsin and chymotrypsin, which are digestive enzymes of the alimentary tract, are identified at page 1 of the specification as serine protease inhibitors. It is clear from the present specification that "resisting a digestive enzyme" refers to inhibiting serine proteases of the alimentary tract. Reconsideration by the Examiner and withdrawal of this rejection is respectfully requested."

These arguments are not found to be persuasive for the following reasons. (i) The claim has not been amended to clarify the recited invention. (ii) The Examiner is confused and does not understand Applicant's argument that "Pepsin, trypsin and chymotrypsin, which are digestive enzymes of the alimentary tract, are identified at page 1 of the specification as serine protease inhibitors". It is well known in the art that pepsin, trypsin, and chymotrypsin are digestive enzymes of the alimentary tract. However, neither the prior art nor the specification, at page 1, identify pepsin, trypsin, or chymotrypsin as serine protease inhibitors. (iii) Applicant's appear to be using the term "resisting" as equivalent with inhibiting; however, a person of ordinary skill in the art would not understand the terms to be equivalent. (iv) Applicant's argument also fails to clarify whether "resisting a digestive enzyme" encompasses only inhibiting serine proteases from the alimentary tract or is intended to encompass inhibiting any hydrolase, any protease, or any serine protease. Therefore, rejection of Claim 20 under 35 U.S.C. 112, second paragraph, is maintained. For purposes of examination, it is assumed that "resisting a digestive enzyme" means inhibiting any serine protease and "a patient in need of treatment" means treatment of any patient in which inhibiting any serine protease would be beneficial.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claims 14, 15, 17, 18, and 20 under 35 U.S.C. 112, first paragraph, for lack of enablement for the reasons described in the prior action, is maintained. In support of their

request that said rejection be withdrawn, Applicants provide the following arguments, which are not found to be persuasive for the reasons provided.

(A) The specification is enabling for treating disseminated vascular coagulation with four anhydridized serine proteases. The claims are enabled if one can extrapolate from this that the entire scope of the claims is enabled.

Reply: The specification fails to enable the full scope of the claims reciting the use of any anhydridized serine protease for treatment of disseminated vascular coagulation (Claims 14, 15, 17, and 18) and treatment of any patient in which inhibiting any serine protease would be beneficial using any anhydridized serine protease (Claim 20), wherein the anhydridized serine protease is a competitive inhibitor. The family of serine proteases is a large and variable family of enzymes with a large number of variable substrates and the potentiality of being involved in many different cellular processes and diseases. The specification fails to teach which of the hundreds of known, naturally occurring serine proteases can be derivitized to produce an anhydridized serine protease that can be used to successfully treat disseminated vascular coagulation or any other condition involving a serine protease. Moreover, the specification fails to teach which of the more than trillions of recombinant proteins with serine protease activity can be derivitized to produce an anhydridized serine protease that can be used to successfully treat disseminated vascular coagulation or any other condition involving a serine protease. The specification also fails to disclose which residues of the trillions of serine protease polypeptides can be derivitized to obtain the desired therapeutic activity. The specification asserts that abdominalgia and hyperamylasemia can be successfully treated with anhydridized digestive enzyme, for example, trypsinogen. However, the specification fails to provide any evidence for

said assertion. In addition, the specification fails to provide any evidence that any condition, other than disseminated vascular coagulation, can be successfully treated with an anhydridized serine protease. Without sufficient guidance, determination of the identity of proteins having the desired biological characteristics, as well as conditions to be treated, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

(B) Applicants do not have to disclose all functioning anhydridized serine proteases, or all residues or regions appropriate for anhydridization, a scheme for modifying any serine protease to obtain the desired function, or how to select successful candidates from all possible choices.

Reply: See (A).

(C) The claims are limited to anhydridized serine proteases capable of inhibiting a serine protease by competitive binding. This excludes inactive species.

Reply: It is acknowledged that the claims are limited to anhydridized serine proteases capable of inhibiting a serine protease by competitive binding. However, the specification fails to teach which of the hundreds of known, naturally occurring serine proteases, or more than trillions of recombinant proteins with serine protease activity, can be successfully derivatized to produce an anhydridized serine protease that is capable of inhibiting a serine protease by competitive binding. Furthermore, the specification fails to disclose which residues should be derivatized or which assay methods, using which active serine proteases or which substrates or binding-partners, should be used to test any said anhydridized serine protease for inhibition of an active serine protease by competitive binding.

(D) Regarding Claim 20, the specification at page 19 provides guidance on how to identify patients in need of treatment.

Reply: It is acknowledged that the specification asserts that patients with abdominalgia or hyperamylasemia are effectively treated with an inhibitor of trypsinogen. However, said assertion does not enable a skilled artisan to use the full scope of the invention, which encompasses treating any patient in need of inhibiting any serine protease with any anhydridized serine protease. Neither the specification nor the claims disclose the full scope of all patients in need of inhibiting a serine protease or how to identify all said patients without undue experimentation.

Written Description

Rejection of Claims 14, 15, 17, 18, and 20 under 35 U.S.C. 112, first paragraph, for insufficient written description, for the reasons described in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. Four actual successful reductions to practice of the invention are shown. One skilled in the art would recognize from this that applicants' were fully in possession of methods using anhydridized serine proteases capable of inhibiting a serine protease by competitive binding. Guidance for identifying patients in need of treatment is found at page 19. From the anhydridization techniques disclosed, one would recognize that applicants' were in possession of the subject matter of claim 20.

These arguments are not found to be persuasive. Methods for anhydridization of proteins is well known in the art; the instant rejection is not based on lack of enablement for anhydridization of proteins. Claims 14, 15, 17, and 18 recite a genus of methods for treating

disseminated vascular coagulation with any anhydridized protein that is a serine protease, wherein anhydridization is on any residue and the anhydridized serine protease is a competitive inhibitor. The four species of methods disclosed fails to describe the recited genus, which encompasses using hundreds of anhydridized known, naturally occurring serine proteases, or more than trillions of recombinant proteins treating disseminated vascular coagulation. Claim 20 recites a genus of methods for any condition, in which inhibiting a serine protease would be advantageous, with any anhydridized protein that is a serine protease, wherein anhydridization is on any residue and the anhydridized serine protease is a competitive inhibitor. It is acknowledged that the specification, on page 19, asserts that abdominalgia and hyperamylasemia can be successfully treated with an anhydridized digestive enzyme, for example, trypsinogen. However, said assertion would not convince a person of ordinary skill in the art that said treatment would be successful. In addition, the specification fails to disclose any other condition, in which inhibition of a serine protease would be beneficial, that can be successfully treated with an anhydridized serine protease, or any anhydridized serine proteases to be used for treatment, or any protocol for treatment. Given this lack of description, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Rejection of Claim 20 under 35 U.S.C. 112, first paragraph, for insufficient written description due to recitation of New Matter is maintained. As stated above, for rejection of Claim 20 under 35 U.S.C. 112, second paragraph, for being indefinite, it is assumed that Claim 20 is meant to recite a method for treating any patient, in which inhibiting any serine protease would be beneficial, with any anhydridized serine protease. The neither the original

specification nor claims disclose said method. Thus, Rejection of Claim 20 under 35 U.S.C. 112, first paragraph, for insufficient written description due to recitation of New Matter is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claims 14-18 under 35 U.S.C. 103(a), as being unpatentable over Wolf et al, 1994 or Berkner et al, 1992 in view of Ashton et al, 1995, is maintained. Claim 20 is herein rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf et al, 1994 or Berkner et al, 1992 in view of Ashton et al, 1995.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. (i) Neither Ashton, et al, Wolf et al, nor Berkner et al teach that enzymatically inactive blood coagulation factors can be used to treat disseminated intravascular coagulation. (ii) The Examiner cites Levi et at. as providing the motivation for doing this. However, Levi et al is not prior art to the present application, which has a 1999 priority date.

These arguments are not found to be persuasive for the following reasons. (i) As stated in the prior action, Wolf et al teach that modified blood factors, which lack protease activity, can be used to prevent or treat thrombosis. A person of ordinary skill in the art would know that thrombosis includes disseminated intravascular coagulation. (ii) The teachings of Levi et al are not necessary for the instant rejection. As stated in the prior action, motivation to use the anhydrothrombin of Ashton et al to treat disseminated vascular coagulation derives from the

desire to reduce mortality in a patient with disseminated vascular coagulation. Levi et al, 2001 merely provides an example of a condition, sepsis, wherein disseminated vascular coagulation occurs. In addition, the teachings of Levi et al, 2001 were known in the art prior to filing of the instant application (Levi et al, 1997).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600